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(71) Applicant *(for all designated States except US)*: UNIVERSITY OF SOUTH FLORIDA RESEARCH FOUNDATION, INC. [US/US]; 4202 East Fowler Avenue, FAO126, Tampa, FL 33620–7900 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SANBERG, Paul, Ronald [US/US]; 11751 Pilot Country Drive, Spring Hill, FL 34610 (US). SHYTLE, Roland, Douglas [US/US]; 1201 Seminole Boulevard #354, Largo, FL 33770 (US). SILVER, Archie, Aaron [US/US]; 13906 Hayward Place, Tampa, FL 33624 (US).

(74) Agent: LUTHER, Barbara, J.; 23930 Jabil Lane, Los Altos Hills, CA 94024–5103 (US).

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(54) Title: NICOTINE ANTAGONISTS FOR NEUROPSYCHIATRIC DISORDERS

(57) Abstract

Neuropsychiatric disorders can be treated by administering a nicotine antagonist, particularly mecamylamine. Combination therapy of mecamylamine with a neuroleptic drug also is disclosed. The neuropsychiatric disorders include Tourette's syndrome, tremors, attention deficit hyperactivity disorder, obsessive–compulsive disorders, schizophrenia, depression, hemidystonia, tardive dyskinesia, Parkinson's Disease and Huntington's Disease (HD).

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NICOTINE ANTAGONISTS FOR NEUROPSYCHIATRIC DISORDERS

BACKGROUND

Field of Use

The present invention is in the field of pharmacotherapy of neuropsychiatric disorders by administering a nicotine antagonist alone, particularly mecamylamine, or in combination with a neuroleptic agent. Examples of such disorders are schizophrenia, bipolar disorder, obsessive compulsive disorder, attention deficit hyperactivity disorder, Tourette's syndrome, and other movement disorders.

Background Information

Tourette's syndrome (TS) is an autosomal dominant neuropsychiatric disorder characterized by a range of symptoms, including multiple motor and phonic tics. It is a hyperkinetic movement disorder expressed largely by sudden, rapid, brief, recurrent, nonrhythmic, stereotyped motor movements (motor tics) or sounds (phonic tics), experienced as irresistible impulses but which can be suppressed for varying lengths of time (Tourette's Syndrome Classification Study Group, Arch Neurol 50: 1013-16). Motor tics generally include eye blinking, head jerking, shoulder shrugging and facial grimacing, while phonic or vocal tics include throat clearing, sniffling, yelping, tongue clicking and coprolalia. The symptoms typically begin in childhood and range from relatively mild to very severe over the course of a patient's lifetime (Robertson MM, Br J Psychiatry, 154:147-169, 1989). Many TS patients also exhibit other neuropsychiatric abnormalities including obsessive compulsive symptoms (Pauls DL et al. Psychopharm Bull, 22:730-733, 1986), hyperactivity and attention deficits (Comings DE, Himes JA, Comings BG, J Clin Psychiatry, 51:463-469, 1990). Problems with extreme temper or aggressive behavior also are frequent (Riddle MA et al. WILEY SERIES IN CHILD AND ADOLESCENT MENTAL HEALTH, Eds. Cohen DJ, Bruun, RD, Leckman JF, New York City, John Wiley and Sons, pp 151-162, 1988; Stelf ME, Bornstein RA, Hammond L, A survey of Tourette's syndrome patients and their families: the 1987 Ohio Tourette Survey, Cincinnati, Ohio Tourette Syndrome Association, 1988), as are school refusal and learning disabilities (Harris D, Silver AA, Learning Disabilities, 6(1):1-7, 1995; Silver AA, Hagin RA, Disorders of Learning Childhood, Noshpitz JD, ed. New York City: Wiley, pp. 469-508, 1990).

While the pathogenesis of TS is still unknown, excessive striatal dopamine and/or dopamine receptor hypersensitivity has been proposed (Singer HS et al. Ann Neurol, 12:361-366, 1982), based largely on the therapeutic effectiveness of dopamine receptor antagonists. TS is frequently treated with the dopamine antagonist haloperidol (Haldol®, McNeil Pharmaceutical, Raritan, NJ), which is effective in about 70% of cases (Erenberg G, Cruse RP, Rothner, AD, Ann Neurol, 22:383-385, 1987; Shapiro AK, Shapiro E, WILEY SERIES IN CHILD AND ADOLESCENT MENTAL HEALTH, Eds. Cohen DJ, Bruun RD, Leckman JF, New York City, John Wiley and Sons, pp. 267-280, 1988). Other neuroleptics include pimozide (Shapiro ES et al. Arch Gen Psychiatry, 46:722-730, 1989), fluphenazine (Singer HS, Gammon K, Quaskey S, Pediat Neuroscience, 12:71-74, 1985-1986), and risperidone (Stamenkovic et al., Lancet 344:1577-78, 1994). An alternative medication frequently employed is the α-adrenergic agonist clonidine, which also is effective for associated attention deficit hyperactivity disorder (ADHD) but has only a 40% success rate for motor and vocal tics (Bruun RD, J Am Acad Child Psychiatry, 23: 126-133, 1984; Cohen DJ et al. Arch Gen Psychiatry 37: 1350-1357, 1980). Other medications that have been used with varying degrees of effectiveness include clonazepam (Gonce M, Barbeau A, Can J Neurol Sci 4: 279-283, 1977), naloxone (Davidson PW et al. Appl Res Ment Retardation 4: 1-4, 1983) and fluoxetine (Riddle MA et al. J Am Acad Child Adol Psychiatry 29: 45-48, 1990). One of the most commonly used medications is haloperidol (Erenberg G, Cruse RP, Rothner AD, Ann Neurol, 22:383-385, 1987). However, therapeutic doses of haloperidol have frequent side effects that affect compliance, including difficulty in concentration, drowsiness, depression, weight gain, parkinsonian-like symptoms – and with long-term use – tardive dyskinesia (Shapiro AK, Shapiro E, Tourette's syndrome and Tic Disorders: Clinical Understanding and Treatment. WILEY SERIES IN CHILD AND ADOLESCENT MENTAL HEALTH. Eds. Cohen, DJ, Bruun, RD, Leckman JF, New York City, John Wiley and Sons, pp. 267-298, 1988). The side effect of tardive dyskinesia is particularly bothersome because it may add additional abnormal, involuntary movements of the tongue, jaw, trunk and/or extremities.

Erenberg et al. (Erenberg G, Cruse RP, Rothner AD, Ann Neurol 22:383-385, 1987) found that most patients with TS stop using their haloperidol or other neuroleptic medications by age 16, often because of these side effects. After TS patients quit medication because of the side effects, they have less control over speech and

movement, which disqualify many for full-time, responsible jobs. The public, including law enforcement officers, often identify the symptoms as intoxication. The unexpected movements and coprolalia cause great social difficulties.

Systemic or intracaudate injections of nicotine have been found to profoundly potentiate reserpine-induced catalepsy in rats (Montgomery SP, Moss DE, Manderscheid PZ, MARIJUANA 84. Eds. Harvey DJ, Paton WDM, Oxford, England, IRL Press, pp 295-302, 1985; Moss DE et al, Life Sci 44: 1421-1525, 1989). Follow-up studies demonstrated that low doses of nicotine could also potentiate haloperidol-induced catalepsy in rats (Sanberg PR et al, Biomedicine and Pharmacotherapy 43: 19-23, 1989; Emerich DF, Norman AB, Sanberg PR, Psychopharmacol Bull 27(3): 385-390, 1991; Emerich DF et al, Pharmacol Biochem Behav 38: 875-880, 1991). These preclinical findings suggested that nicotine might also potentiate the therapeutic properties of neuroleptics in treating hyperkinetic movement disorders such as TS.

In a preliminary clinical trial, ten TS patients continued to receive haloperidol and added chewing Nicorette® nicotine (2 mg) gum. The patients had rapid, striking and marked relief from tics and other TS symptoms which were not optimally controlled by haloperidol alone (Sanberg PR et al, Biomedicine and Pharmacotherapy 43:19-23, 1989). In two subsequent studies, nicotine gum reduced tics in patients already receiving haloperidol, while placebo gum had no effect (McConville BJ et al, Am J Psychiatry 148:793-794, 1991; McConville BJ et al, Biological Psychiatry, 31:832-840, 1992). However, the benefits of the gum were short lived (1-4 hours), and the bitter taste and gastrointestinal side effects limited compliance (McConville BJ et al, Biological Psychiatry 31:832-840, 1992).

The 7 mg, 24-hour transdermal nicotine patch (Nicoderm® TNP) was tested in 11 TS patients who were not responding optimally to current neuroleptic treatment (Silver AA et al. The Effects of Nicotine on Biological Systems II. PBS Clarke, M. Quik and K. Thurau, (Eds.); ADVANCES IN PHARMACOLOGICAL SCIENCES, Birkhauser Publishers, pp. 293-299, 1995). Patients' tics were videotaped before treatment began and 3 hours after the start of treatment. The frequency and severity of tics were reduced 47% and 34%, respectively, at three hours. Patients with the least control by neuroleptic treatment showed more dramatic improvement than did patients whose neuroleptic treatment alone had been more effective. The effects of the TNP persisted longer than

the expected 24 hours. In two patients with incapacitating TS symptoms before the TNP, the effect lasted 3 weeks to 4 ½ months without further administration of nicotine.

To further explore the potential long-term therapeutic response to TNP in TS patients, twenty TS patients (17 children and adolescents and 3 adults), in 18 of whose tic symptoms were not controlled with neuroleptics and 2 of whom were free of medication, were followed for various lengths of time following the application of two TNPs (Silver AA et al. J Amer Acad Child & Adolescent Psychiatry, 35(12): 1631-1636, 1996; Shytle RD et al. Drug Development Research, 38(3/4): 290-298, 1996). While there was a broad range of individual responses, it was determined that each application of a single TNP produced a significant reduction in Yale Global Tic Severity Scale mean scores lasting approximately 1-2 weeks. Thus, transdermal nicotine was an effective adjunct to neuroleptic therapy of TS, and helped when administered alone to two patients.

It has been observed that 50% of children presenting with TS also have Attention Deficit Hyperactivity Disorder (ADHD). ADHD is a neurobiological disorder characterized by impaired attentiveness, increased impulsivity, and hyperactivity. ADHD is now the most commonly diagnosed childhood psychiatric condition, with some 3.5 million afflicted. In addition, 60% of adolescents with ADHD continue to have symptoms in adulthood, representing another 2.5 million patients.

The current patent application is concerned with the administration of nicotine antagonists, particularly mecamylamine (3-methylamino-2,2,3-trimethylnorcamphane). Mecamylamine is well known as a nicotine antagonist and blocks ganglia which nicotine stimulates. First introduced as an anti-hypertensive, mecamylamine blocks sympathetic ganglia transmission and thereby causes vasodilatation and a fall in blood pressure (Taylor P, In: Goodman LS, Gilman A (eds) THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, McMillan Publishing Co., New York City, pp 193-95, 1996). Generalized ganglionic blockade may result also in atony of the bladder and gastrointestinal tract, impaired sexual function, cycloplegia, xerostomia, diminished perspiration and postural hypotension. While the clinical use of mecamylamine as a ganglionic agent has largely been replaced by more effective antihypertensive medications, scientists remain interested in mecamylamine because of its ability to block nicotine binding sites in the brain (see, e.g., Martin BR, Onaivi ES, Martin TJ, Biochemical Pharmacology 38: 3391-3397, 1989; and Banerjee S et al, Biochemical

Pharmacology 40(9): 2105-2110, 1990). These nicotine binding sites, known as nicotinic acetylcholinergic receptors (nAChr), are normally activated in the brain by acetylcholine, a prominent neurotransmitter.

Nicotine, via tobacco in various forms, has been one of the most widely utilized drugs for centuries (Wilbert J, J Ethnopharmacol 32(1-3): 179-186, 1991). Nicotine is a potent modulator of nAChrs (Changeux JP, Sci Amer (November) pp 58-62, 1993). Through these receptors, nicotine activates the presynaptic release of several neurotransmitters including acetylcholine, norepinephrine, serotonin and dopamine (Balfour DJK, Pharmacological Therapeutics 16: 269-282, 1982). Agents which can modulate central monoaminergic neurotransmissions by acting on nAChrs may be useful therapeutically for treating neuropsychiatric disorders (Jarvick ME, Br J Addict 86: 571-575, 1991; Newhouse PA, Hughes JR, Br J Addict 86: 521-526, 1991; and Hughes J, Clarke PBS (Eds): The effects of nicotine on biological systems II. Abstract S40, 1994; Decker MW et al, Life Sci 56: 545-570, 1995).

Unlike some ganglionic blocking agents, which do not readily reach the central nervous system (CNS), mecamylamine has been reported to produce central effects in humans, such as blocking the CNS actions of nicotine (Martin BR, Onaivi ES, Martin TJ, Biochemical Pharmacology 38:3391-3397, 1989) and in altering cognitive functioning (Newhouse PA et al, Neuropsychopharmacology 10: 93-107, 1994), electrical brain waves (Pickworth WB, Herning RI, Henningfield JE, Pharmacology Biochemistry & Behavior 30: 149-153, 1988) and cortical blood flow (Gitalman DR, Prohovnik I, Neurobiology of Aging 13: 313-318, 1992).

While most animal studies used more than 0.5 mg/kg, Driscoll found that a small dose of only mecamylamine (<0.3 mg/kg, not 0.5 mg/kg) to high-avoidance rats increased their avoidance success almost as much as 0.1 mg/kg nicotine (but less than 0.2 mg/kg nicotine). Based on his experiments, Driscoll concluded that "mecamylamine may exert unpredictable effects on rats at the dosage levels used to block nicotine in behavioral tests" (Driscoll P., Psychopharmacologia (Berl.) 46:119-21, 1976).

In a recent study of the nicotine receptor (nicotine binding site) and its ion channel (mecamylamine binding site), Banerjee et al. disclosed that mecamylamine and several nicotine analogs have a high affinity for the mecamylamine site. Like mecamylamine, several nicotine analogs also have anti-nicotinic effects (Banerjee S et al. Biochem Pharmacol 40(9): 2105-10, 1990). Research is also proceeding on alkaloids

which act on the nicotinic receptor channels (Daly JW: Alkaloids as Agonists, Antagonists and Noncompetitive Blockers of Nicotinic Receptor Channels. In: PROCEEDINGS OF NICOTINIC ACETYLCHOLINE RECEPTORS AS PHARMACEUTICAL TARGETS. July 24-25, 1997, Washington, DC).

Many neuropsychiatric disorders involve abnormal or involuntary movements including but not limited to obsessive-compulsive disorder (OCD), TS, ADHD, hemidystonia, Parkinson's disease, and Huntington's disease. These diseases may be caused by neurochemical imbalances in the brain's basal ganglia. Acetylcholine, by activating nAChrs in the basal ganglia regulates motor activity in humans. The action of nAChrs in the basal ganglia has been well documented (Clarke PBS, Pert A, Brain Res 348: 355-358, 1985). Nicotinic stimulation excites activity in the dopamine (DA)-producing cells in the basal ganglia (Clarke PBS et al, J Pharmacol Exper Therapeutics 246: 701-708, 1988; Grenhoff J, Aston-Jones G, Svennson TH, Acta Physiol Scand 128: 351-358, 1986; Imperato A, Mulas A, Di Chiara G, Eur J Pharmacol 132: 337-338, 1986), while mecamylamine blocks nAChr and inhibits DA release from basal ganglia structures (Ahtee L, Kaakkola S, Br J Pharmacol 62: 213-218, 1978).

U.S. Patent No. 5,774,052 to Rose and Levin discloses agonist-antagonist combinations to reduce the use of nicotine and other drugs. In combination with nicotine, the nicotinic antagonist mecamylamine was given to treat tobacco dependency. Rose and Levin proposed including both nicotine and mecamylamine in a patch. Rose and Levin also suggested that such agonist-antagonist combinations could be used in other psychopathological disorders and cases involving neuronal dysfunction (e.g., manic depression, schizophrenia and hypertension due to sympathetic autonomic disorder).

It would benefit patients to be able to have better symptom control and fewer side effects. In particular, it would be preferable to take a single drug, as did patients in the reports disclosed herein. Our clinical experience with mecamylamine in human patients with a variety of diagnoses supports a variety of uses. Herein is disclosed improved symptom control with a nicotine antagonist (mecamylamine) alone or in combination with neuroleptics for the treatment of a variety of neuropsychiatric disorders.

SUMMARY OF DISCLOSURE

It is an object of the present invention to provide new therapy for patients with neuropsychiatric disorders.

It is a further object of the present invention to provide therapy with fewer side effects to improve patient compliance with taking their medication as well as to improve their quality of life and social functioning.

Herein is disclosed a method of treating an individual with neuropsychiatric disorders comprising administering to the individual an effective amount of a nicotine antagonist. Preferably, the nicotine antagonist is mecamylamine or a stereoisomer or an analog thereof. The effective amount of mecamylamine is that which improves the individual's signs and symptoms. In movement disorders, the effective amount is the amount which decreases the frequency or severity of tics in the individual. Additionally, there may be an additional step of administering to the individual an effective amount of a neuroleptic drug. Examples of neuroleptic drugs are haloperidol, pimozide, fluphenazine, and risperidone.

Preferably, the treated neuropsychiatric disorder is nicotine responsive. Examples of nicotine-responsive disorders are movement disorders such as Tourette's Syndrome, essential tremors, hemidystonia, tardive dyskinesia, Parkinson's Disease and Huntington's Disease (HD). Examples of other nicotine responsive disorders are schizophrenia, depression, attention deficit hyperactivity disorder, and obsessive-compulsive disorder.

Also disclosed is a method of treating an individual having Tourette's Syndrome comprising administering to the individual an effective amount of mecamylamine. In a further embodiment, there is a method of treating an individual having Tourette's Syndrome which comprises administering to the individual an effective amount of a nicotine antagonist. Examples of nicotine antagonists are mecamylamine and other compounds disclosed below.

DESCRIPTION OF DRAWINGS

Figure 1 shows the chemical structures of mecamylamine and several other nicotinic antagonists.

DETAILED DESCRIPTION

We have demonstrated that nicotine, when added to continuing haloperidol neuroleptic treatment, produced rapid and marked relief from tics and other symptoms of TS not controlled by neuroleptics alone. Using neuroleptic-induced catalepsy as a model for understanding the therapeutic actions of neuroleptics and nicotine in TS patients, it was initially proposed that nicotine potentiates the actions of D2 antagonists on catalepsy by activating disinhibited striatal cholinergic interneurons which innervate striatopallidal GABA projection neurons. Thus, an additive inhibition of the globus pallidus (Emerich DF et al, Pharmacol Biochem Behav 38:875-880, 1991) is produced. However, because nicotine has complex neuropharmacologic actions, the exact mechanism by which nicotine interacts with neuroleptics to reduce symptoms of TS has been difficult to elucidate. One hypothesis is that nicotine transdermal nicotine exerts its therapeutic effect by causing persistent inactivation of the nicotine receptor (Shytle RD et al, Drug Development Research 38(3/4):290-298, 1996). A neuropharmacological action consistent with this hypothesis has been observed in vitro (Lukas RJ, Drug Dev Res 38:136-48, 1996).

In a few TS patients who were not responding to the usual treatments, we found that mecamylamine, the nicotine receptor antagonist, formerly approved for the treatment of hypertension (Inversine®, Merck & Co., West Point, PA), also reduced the symptoms of TS. The improvement in TS symptoms following mecamylamine treatment alone or in combination with neuroleptics was unexpected since one would generally expect the effects of mecamylamine to oppose those of nicotine: If fewer tics occur with nicotine, one would expect more tics with mecamylamine. Thus, the significant improvement seen in patients with mecamylamine treatment is a surprising development. We believe that in addition to mecamylamine, other nicotine receptor antagonists, discussed in detail below, also could be used. Furthermore, based on effects on co-existing illnesses, we believe that nicotine receptor antagonists are useful not only in TS, but also in such other neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD), Obsessive Compulsive Disorder (OCD), Essential Tremor (ET), Tardive Dyskinesia (TD), Parkinson's Disease (PD), Depression (D) and Huntington's Disease (HD). Nicotine antagonists can also be expected to affect other nicotine-responsive disorders (e.g., schizophrenia, bipolar disorder, and panic states).

Hemidystonia also is nicotine responsive and is a focal movement disorder involving an arm and a leg on one side of the body. It generally develops in adulthood, remains stable and rarely spreads to other body parts. It is part of a family of syndromes which also include spasmodic torticollis (intermittent spasms turning or bowing the head). In generalized and segmental dystonias, involving more of the body, anticholinergic drugs, benzodiazepines, baclofen, carbamazepine, reserpine and levodopa have been tried for relief of symptoms. In severe focal dystonias, a dilute solution of botulinum toxin may be injected into the affected muscle, or nerves may be denervated surgically. Hemidystonia can also be expected to respond to mecamylamine.

Definitions:

"Nicotine Antagonists", of which mecamylamine is but one example are a large and growing category. A truly exhaustive list of such compounds would take up too much space here. The following discussion is not intended to be exhaustive but to teach how to identify compounds which are encompassed by this term. Currently interesting nicotinic antagonists and related compounds in research were discussed by Daly JW (*ibid*) which is incorporated by reference. Clark and Reuben (Br. J. Pharmacol. 117: 595-606, 1996) disclose dihydro-beta-erythroidine, methyllycaconitine, chlorisondamine, and trimethaphan. Normecamylamine, N-(1,2,2)trimethyl-1-bicyclo[2,2,1,]-heptylbenzenamine, dimethylaminoisocamphane, exo-aminonorbornane, 2,2,6,6-tetramethylpiperdine, 2,2,6,6-tetramethyl-4-aminopiperdine, and pempidine were identified as active nicotinic antagonists (Banerjee et al., Biochemical Pharmacology 40: 2105-2110, 1990). This article and its test methods are hereby incorporated by reference. Additional examples of nicotine antagonists include erysodine (Decker, European Journal of Pharmacology 280:79-89, 1995), phenyltropane carboxylic acid methyl esters (Lerner-Marmarosh et al., Life Sciences 56(3): PL 67-70, 1995), arylpempidine analogues (Wang et al., Life Sciences 60(15):1271-1277, 1997); ibogaine (Daly, Biochemical Pharmacology 40(9):2105-10, 1990).

In addition, the various stereoisomers and substituted analogs of mecamylamine have been tested for activity (Stone et al., J Med Pharm Chem 5(4);665-90, 1962, hereby incorporated by reference). Activity, as tested in rats by nicotine convulsions and pupil dilatation, was routinely lost with larger substitutions for the methyl groups. Both methyl or dimethyl groups on the amino group were more active than other

substituents. The *d* form was active; however, the *dl* racemate appeared to be slightly more active. Consequently, we are postulating that the *l* form has significant activity in this use of mecamylamine. Stone et al. reported that the *exo* form (methylamino group lies on the same plane as the methylene bridge) was always stronger than the *endo* form (methylamino group lies below the methylene bridge and tends to lie within the cage created by the bridge). In addition, a partial structure, 2,2,-dimethyl-3-methylaminobutane, also was active. Slight differences in activity between different models for the *d* form and other analogs indicates that there may be differential activity and effectiveness in neuropsychiatric disorders.

Other compounds which may reasonably be expected to be active in this use are disclosed in U.S. 4,837,218 (Alkylated Bicycloalkaneamines for Neurotoxic Injury), U.S. Patent No. 2,894,987 (N-allyl-2-aminoisocamphane), U.S. Patent No. 3,148,118 (Analeptically Active Agents), U.S. Patent No. 3,164,601 (Analeptically Active N-Substituted Aminonorcamphane Derivatives). These patents are incorporated by reference.

"Beneficial effect" is an observable improvement over the baseline clinically observable signs and symptoms. For example, a beneficial effect in motor disorders includes decreases in tic frequency or severity, but improvements also can be manifested indirectly through reductions in anxiety, aggressive outbursts, and premonitory urges which often precede or compound the severity of abnormal movements. Treatment effects can be quantified by clinical observations and video tape scoring. Beneficial effects in obsessive compulsive disorders include diminution in the obsessive or compulsive behavior, which can be confirmed by patient's reports. Suemaru et al (*ibid*) has proposed that the nicotine-induced rat tail tremor can be used to screen for compounds to treat tremors. Repeated nicotine administration can induce locomotor hyperactivity and a tail tremor in rats which is blocked with mecamylamine (0.1 – 1 mg/day, ip) but not by hexamethonium which does not readily enter the brain. Centrally active clonidine (α-adrenergic agonist) and prazosin (α-adrenergic antagonist) reduced tail tremor more markedly than hyperactivity. However, centrally active haloperidol and chlorpromazine (dopaminergic antagonists) reduced hyperactivity more markedly than tail tremor (Suemaru K., Oishi R, Gomita Y, Arch Pharm 350:153-57, 1994).

The Yale Global Tic Severity Scale (YGTTS) is the most widely used clinical assessment rating scale used to assess tic symptoms. It provides an objective measure of

tic frequency of severity based on clinical observations. This scale includes a tic symptom inventory which is filled out based on the patient's personal recall of tics occurring over the previous week. Using this inventory as a guide, the clinician then rates the severity of both motor and vocal tics on five separate dimensions: number, frequency, intensity, complexity, and interference. In addition, there is also a separate rating of global impairment which characterizes the impact of the disorder on the patient's social function, self esteem, etc., over the previous week.

An objective method for rating tic symptoms employs video recording of patients. A videotape of at least five minutes is viewed and the frequency and severity of both motor and vocal tics are recorded. Video taping has proven a valuable adjunct to clinical rating systems for drug trials (Leckman JF, et al., Arch Gen Psychiatry, 48: 324-328, 1991; Shapiro ES, et al., Arch Gen Psychiatry, 46: 722-730, 1989; McConville BJ, Fogelson MH, Norman AB, Klykylo WM, Manderscheid MA, Parker KW, Sanberg PR, Am J Psychiatry, 148: 793-794, 1991; Silver AA, Shytle RD, Philip MK, Sanberg PR, The Effects of Nicotine on Biological Systems II. PBS Clarke, M. Quik and K. Thurau, (Eds.); Advances in Pharmacological Sciences, Birkhauser Publishers, pp. 293-299, 1995; Reveley MA, et al., Journal of Psychopharmacology Supplement, A30, 117, 1994) and challenge studies (Chappell PB, et al., Adv Neurol 58: 253-262, 1992; Lombroso PJ et al. Neurology 41: 1984-1987, 1991). In a recent report, Chappell and colleagues (Chappell PB, et al. J Am Acad Child Adolesc Psychiatry, 33: 386-393, 1994) validated both motor and vocal tic frequency by video tape and found that such data correlated well with established clinical rating scales.

Neuroleptic drug as used herein is a drug which affects thinking, feeling and neurological status, particularly movement and posture (as in TS and Parkinson's disease). Almost all neuroleptic drugs have a strong extrapyramidal effect, resulting in Tardive dyskinesia (see above). Examples of neuroleptic drugs are haloperidol (Haldol®, McNeil Pharmaceutical, Raritan, NJ), pimozide (Orap®, Teva Pharmaceuticals, Kulpsville, PA), fluphenazine, and risperidone (Risperdal®, Janssen Pharmaceutical, Titusville, NJ).

The term "effective amount" refers to the amount of nicotine antagonist that is necessary to provide benefit. The precise amount required will vary depending upon the particular compound selected, the age and weight of the subject, severity of the disorder, route of administration, and so forth, but may easily be determined by routine

experimentation, as described below in the clinical examples. In general, however, an effective amount will range from about 0.001 mg/kg to about 6 mg/kg per day, preferably about 0.002 mg/kg to about 3 mg/kg, more preferably about 0.005 mg/kg to about 2 mg/kg, and most preferably about 0.01 to about 1.5 mg/kg. A starting dose for adults with drug-resistant TS is about 2.5 mg per day, with dosage adjusted according to return of symptoms (see case histories below). A small child with mild ADHD preferably starts with 1 mg per day or less. The effective amount of a neuroleptic drug is the least amount which when combined with a nicotine antagonist relieves symptoms. Our clinical experience suggests some patients may not require any neuroleptic drug to achieve maximum benefit.

The term "pharmaceutically acceptable" refers to a lack of unacceptable toxicity in a compound, such as a salt or excipient. Pharmaceutically acceptable salts include inorganic anions such as chloride, bromide, iodide, sulfate, sulfite, nitrate, nitrite, phosphate, and the like, and organic anions such as acetate, malonate, pyruvate, propionate, cinnamate, tosylate, citrate, and the like. Pharmaceutically acceptable excipients are described at length by E.W. Martin, in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Pub. Co.).

Pharmaceutical compositions containing nicotine antagonists may contain one or more pharmaceutical carriers. The term "pharmaceutically acceptable carrier" refers to any generally acceptable excipient that is relatively inert, non-toxic and non-irritating. When the carrier serves as a diluent, it may be solid, semisolid, or liquid material acting as a vehicle, excipient, or medium for the active ingredient. Pharmaceutical unit dosage forms may be prepared for administration by any of several routes, including, but not limited to, oral and parenteral (especially by intramuscular and intravenous injection, or by subcutaneous implant or transdermal administration). Representative of such forms are tablets, soft and hard gelatin capsules, powders, lozenges, chewing gums, emulsions, suspensions, syrups, solutions, sterile injectable solutions, and sterile packaged powders. Compositions containing nicotine antagonists may be formulated by procedures known in the art so as to provide rapid, sustained, or delayed release of any or all of the compounds after administration.

As the nicotine antagonist formulation of the present invention is well suited to oral administration, preferred carriers facilitate formulation in tablet or capsule form. Solid pharmaceutical excipients such as magnesium stearate, calcium carbonate, silica,

starch, sucrose, dextrose, polyethylene glycol (PEG), talc, and the like may be used with other conventional pharmaceutical adjuvants including fillers, lubricants, wetting agents, preserving agents, disintegrating agents, flavoring agents, and binders such as gelatin, gum arabic, cellulose, methylcellulose, and the like, to form admixtures which may be used as such or may be tabulated, encapsulated, or prepared in other suitable forms as noted above. A general description of formulation is given in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Pub. Co.).

Administration

Administration is preferably by oral dosage but may be by transdermal application, intranasal spray, bronchial inhalation, suppository, parenteral injection (e.g., intramuscular or intravenous injection), and the like. Carriers for parenteral administration include, without limitation, aqueous solutions of dextrose, mannitol, mannose, sorbitol, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-polyoxypropylene block polymers, and the like. One may additionally include suitable preservatives, stabilizers, antioxidants, antimicrobials and buffering agents, for example, BHA, BHT, citric acid, ascorbic acid, tetracycline, and the like. Alternatively, one may incorporate or encapsulate the nicotine antagonist formulation in a suitable polymer matrix or membrane, thus providing a sustained-release delivery device suitable for implantation or application to the skin. Other devices include indwelling catheters and devices such as the Alzet® minipump.

The invention has been disclosed by direct description. The following are examples showing the efficacy of the method in providing benefit. The examples are only examples and should not be taken in any way as limiting to the scope of the method.

EXAMPLES

Clinical Examples

Patient 1 was a tall, 173-pound, 15-year-old male diagnosed with TS. He had been a patient in our clinic, receiving 2 mg of haloperidol daily and two transdermal nicotine patches (14 mg/24 hrs) each week for approximately one year for effective control of severe symptoms of TS. However, approximately two months before his scheduled follow-up visit, his tics, which had been under excellent control, had emerged

again. At that time, his haloperidol dose was increased to 3 mg/day and the frequency of nicotine patch application was increased to every other day, with some improvement noted. However, the side effects of the nicotine patch, particularly nausea, were disturbing to the patient, resulting in his refusal to wear the patch. In addition, because of the increased risk of nicotine addiction with daily use, we were reluctant to subject the patient to continued use of the patch.

Two weeks before his visit to our clinic, the nicotine patch was discontinued. Eye-blinking, eyebrow raising, facial grimacing, head jerks, abdominal tics, and leg/foot movements were present. His score on the YGTSS was 17/30; his tics totaled 245 over a 5 minute period with overall severity rated as 3 (moderate) on a 7-point scale.

Mecamylamine (5 mg) was given orally at about 11:30 AM. Approximately two hours later, the patient reported that his urge to tic was reduced. The YGTSS score was 6/20, and though tics were still present, there was a 25% decrease in tic frequency. Overall tic severity was reduced by 50%. By 6:00 PM, his mother reported that the patient felt better, there were virtually no tics present, and there were no side effects. However, by the next morning, his tics were beginning to return. One month later, on a daily dose of 5 mg mecamylamine at breakfast, his tics were still under control, and the patient reported that he was more relaxed and alert. The shy, taciturn youth of 30 days earlier was now more outgoing and voluble.

The clinical experience of treating this patient indicated that, in combination with haloperidol, mecamylamine could be used to suppress motor tics. The effect of mecamylamine after a single oral dose was seen in 2-3 hours and lasted approximately 8-12 hours.

Patient 2 was a 16-year-old in the ninth grade whose overall cognitive functioning was in the high-average range but with severe deficit in visual-motor function. He developed motor and vocal tics at 10 years of age, within six months after starting on methylphenidate and Dexedrine® (dextroamphet-amine sulfate, SmithKline Beecham Pharmaceuticals, Philadelphia, PA) for attention deficit disorder and academic difficulty. With 0.1 mg of clonidine three times a day, his tics were said by his parents to be under control. However, for the past two years, he has taken no medication for motor and vocal tics. By the end of eighth grade, he had failed math, received C and D grades in his other subjects and had marked difficulty with any visual-motor function. His handwriting was slow and labored; he resisted any written work, became frustrated

with it, and felt that he was doomed to failure. On his visit to our clinic, his tics were clearly evident: eye blinking, mouth grimacing, gross body tics, quick and jerky movements of his shoulders, head tics, and sniffing. He complained that he was "active in his head" (distractible). During the summer he was attempting to learn math so that he could retake the examination and enter high school in the fall. However, he was having difficulty writing down the steps needed to answer the math problems (as is required in the examination) although he can "get the steps in his head." He has been impatient, frustrated and giving up.

Mecamylamine (5 mg) was prescribed and the patient was told to take it after dinner. His mother, a nurse, reported that two hours later he started to study math. This time, he was patient, felt his "mind is clearer", was more relaxed, and worked on math problems for three hours without distraction. His tics had subsided in intensity and frequency. The following morning, he felt restless, and tics started to return, though not as disturbing as previously. He had eye blinking and gross, jerky body movements. He was prescribed 5 mg mecamylamine at breakfast and 2.5 mg after dinner daily. Twelve days later, the patient reported that with the medication, he was not "hyper" and could concentrate on his school work. The tics, although occasionally present, had subsided. His blood pressure was unchanged at 114/80. In this patient, no neuroleptic drugs were given in combination with mecamylamine, which suggests that mecamylamine given alone can suppress TS symptoms. After eight weeks of treatment, the patient's mother reported that he was doing fine and wanted to continue therapy and had entered high school.

Patient 3 was a 35-year-old, who has had TS with severe motor and vocal tics, obsessions and compulsions since the age of six. She is the mother of three children, the oldest of whom a girl aged 12 who also had TS. A variety of medications were tried, including Zoloft® (sertraline hydrochloride, Roerig Div, Pfizer, New York City) for several years to limit her depression and mood swings. In June 1996, with a trial of the transdermal nicotine patch (7 mg) given in our clinic, her tics subsided within three hours. However, in the next 24 hours, knee, ankle and wrist joints became painful and swollen; and the patch was discontinued. A trial dose of haloperidol (0.5 mg) was then given. In 12 hours, she experienced a precipitous rise in temperature which necessitated discontinuation of haloperidol. On follow-up at our clinic one year later, she was tense

and unhappy, with multiple and severe tics, almost continual eye blinking, grimacing, nose twitching, sniffing, compulsive need for everything to be "just right" in her home.

She was started on 5 mg mecamylamine at 2 PM. At 5 PM there was a distinct obtundation of tics which, although still present, were markedly reduced (50%) in intensity. She was continued on 5 mg mecamylamine for 4 days and reported that the tics were still present but less intense. She reported feeling relaxed with decreased anxiety. Moreover, she reported that her urges to have "rage outbursts" during stressful situations were reduced while taking the mecamylamine. The daily dose of mecamylamine was continued for 30 days with no appreciable change in blood pressure or heart rate. She complained of constipation during her menses, but reported no other side effects. When her prescription for mecamylamine ran out, she requested that the mecamylamine be continued. In this patient, as with patient 2, a neuroleptic was not necessary.

Patient 4 was a 43-year-old salesman with a history of TS since age 14. He was receiving haloperidol (0.5 mg bid) and a 14 mg transdermal nicotine patch every 3d day each week for the previous 6 months, without complete control of motor or vocal tics. Rather than increase the haloperidol dose or increase the frequency of nicotine patch, the nicotine patch was discontinued and mecamylamine (5 mg per day) was prescribed. At baseline, the YGTSS was 27/30, and a 5-minute segment of videotape revealed a total tic count of 207 with an overall severity of 4 (very noticeable) on a 7-point scale. Approximately 90 minutes after the first dose of mecamylamine, the patient reported that he felt more relaxed; his YGTSS score was 20/20; and severity was 2.5 (slightly noticeable). Six hours later, the patient reported that his feeling of relaxation persisted, and the facial grimacing and head jerks were not apparent. His eye blinking, although still occurring, was decreased in severity. However, by the next morning, the tics were beginning to return. With 5 mg mecamylamine at breakfast, obtundation of tics within 1-2 hours was again apparent. Approximately eight hours later the tics began to return. An additional dose of 2.5 mg mecamylamine before dinner was prescribed. This dose controlled motor and vocal tics during the evening. A maintenance dose of 5 mg mecamylamine with breakfast and 2.5 mg before dinner was prescribed. Haloperidol (0.5 mg bid) was continued. Nicotine was discontinued. The combined therapy of mecamylamine and haloperidol, each in small doses, controlled motor and vocal tics.

Recently patient 4 reported that his other physician could not find a cause for his chronic tiredness which had started before mecamylamine treatment. The patient discontinued mecamylamine and resumed the nicotine patch.

Patient 5 was an 18-year-old male who was first seen in our clinic at age 15. His TS symptoms had been treated with pimozide (Orap®, Teva Pharmaceuticals, Kulpsville, PA) up to 16 mg daily since age 10. He had a strong family history of tic spectrum disorders: His mother, maternal grandfather, maternal uncle and a male cousin all had evidence of Tourette symptoms. At his initial clinic visit, he was receiving 12 mg of pimozide together with Prozac® (fluoxetine hydrochloride, Eli Lilly & Co., Indianapolis IN). His motor tics were minimal but he was depressed with severe Parkinsonian-like facies and a fine motor tremor of his hands aggravated by intention. Decreasing pimozide to 4 mg daily and discontinuing Prozac resulted in relief of both depression and Parkinsonian-like symptoms, except for the persistent hand tremor. During the course of his treatment with us, an abnormal EEG with mild background disorganization and sharp activity lateralized to the left temporal region was found. He was treated with carbamazepine, haloperidol and Cogentin® (benztropine mesylate, Merck & Co., West Point, PA) with marked reduction in motor and vocal tics. However, the tremors persisted, and obsessive and compulsive symptoms became prominent. He said he could not focus on a task because his mind was "wandering to something else". A trial of nicotine patch resulted in nausea, headache and noncompliance. Two months later on a visit to the clinic, a trial of mecamylamine 2.5 mg was given. Within two hours, this patient said, "I feel really calm", and he said feeling like this, he could go back to his community college studies. In addition, the hand tremor, so pronounced before mecamylamine administration, had almost disappeared.

Patient 6 was a 23-year-old male, who had had severe Tourette symptoms since he was in second grade. Over the years he had been treated with a variety of neuroleptic medications as well as clonidine and clonazepam (Klonopin®, Roche Laboratories, Nutley, NJ.) At his first visit to our clinic, he had been receiving 12 mg of pimozide daily for at least two years, and was working as a counselor at a camp for emotionally disturbed children. On two separate occasions, he had failed his courses at a community college to become an Emergency Medical Technician. His Tourette symptoms were among the most severe seen at our clinic. He was in constant restless motion, his speech was under pressure, there were tic-like grimaces on his face, shrugging of his shoulders,

copropraxia (his fingers darting to his groin), but most prominent was coprolalia: Every other word was punctuated with an expletive, sexual in nature, under pressure, distinct, and loud. He tried to cover up using a smile and joviality, but he was frightened and depressed, with a significant tremor of his fingers. On neuropsychological testing, severe visual-motor problems were evident. A trial of 7 mg transdermal nicotine resulted in a mild decrease in intensity of his tics and coprolalia. However, within 4 hours he became nauseous and dizzy. Nicotine patch was tried daily for one week increasing the time it was applied, but side-effects continued, and nicotine was discontinued.

After a 2-week washout of nicotine, 2.5 mg mecamylamine daily was prescribed. At the end of 7 days, the patient reported that about 70% of his coprolalia had subsided. Follow-up at that time confirmed not only the significant decrease in coprolalia, but now what remained was whispered. His restlessness too subsided as did the facial grimaces. Only a trace of hand tremor remained.

Patient 7 was a 16-yr-old female with TS, obsessive-compulsive disorder and depression. She was given 2.5 mg of mecamylamine and 25 mg of Zoloft and has been treated for one month. Her mother reported that "she is doing pretty well." The patient's neck jerks stopped after 2-3 days on medication. The patient was no longer depressed, laughed more and got along better with others. Her daytime mood swings improved about 60%. Her mother stated that she had continued to improve in the third and fourth weeks.

Summary of Findings: In all cases improvement in symptoms was seen. All patients reported feeling more "relaxed" (one too relaxed). The two female patients' mood swings were decreased on medication. At the doses administered, there were no significant blood pressure changes. Because mecamylamine at higher doses is approved for hypertension, the lower doses should be well tolerated. These patients had multiple problems: Besides TS, patient 2 had ADHD and obsessive thoughts which were both helped by the new therapy; and patients 3 and 7 also had compulsive behavior which decreased with mecamylamine treatment. In addition, patient 5 had a tremor of the hand which was reduced following mecamylamine administration. Therefore, mecamylamine has been beneficial in reducing symptoms of inattention, hyperactivity, tremors, obsessive compulsive behavior, depression and mood swings, in addition to the motor and vocal tics of Tourette's syndrome.

Dosages for these TS patients whose condition was not treatable with conventional therapy are summarized below in Table 1. Dosages ranged from about 0.03 - 0.10 mg/kg. This range was used to calculate Table 2.

Table 1. Tested Therapeutic Doses of Mecamylamine (Inversine®)

Sex	Diagnosis	Age	Daily Dose (mg)	Weight (lbs.)	(kg)	mg/kg
M	TS	15	5	173	78.64	0.06358
M	TS	44	5	183	83.18	0.06011
F	TS,OCD,D	35	5	131	59.55	0.08397
M	TS	18	2.5*	152	69.09	0.036
M	ADHD, TS	16	7.5	163	74.09	0.10123
M	TS	36	2.5	155	70.45	0.03548
M	ADHD, TS	14	2.5	170	77.27	0.03235
M	TS	23	2.5	146	66.36	0.03767
F	TS,OCD,D	16	2.5	125+	56.81	0.044

* While 2.5 mg/day effectively controlled hand tremors in this patient, reducing the daily dose to 1.25 mg/day resulted in a return of tremors.
+Estimated

Table 2. Estimated Therapeutic Dose Ranges According to Body Weight

Body Weight	Daily Therapeutic Dosage Range* (mg)	
(lbs.)	Low dose (mg)	High dose (mg)
55	0.75	2.5
75	1	3.5
95	1.25	4.5
115	1.75	5
135	2	5.5
155	2.25	6.5
175	2.5	7.5
195	2.75	8.5
215	3	9.5

*Based on the tested range of 0.03 - 0.10 mg/kg

Other Uses

Recent reports suggest that nicotine reduces the motor symptoms of Parkinson's disease (Fagerström KO et al, Psychopharmacology 116: 117-119, 1994), the cognitive deficits found in Alzheimer's disease (Newhouse PA et al, American Journal of Psychiatry 143: 1494-1495, 1986), the symptoms of schizophrenia (Adler LE et al, Am J Psychiatry 150: 1856-1861, 1993), Attention Deficit Hyperactivity Disorder (ADHD) (Levin ED et al, Psychopharmacology 123: 55-62, 1995) and depression (Salín-Pascual RJ et al, Psychopharmacology 121(4): 476-479, 1995). While it is generally believed that nAChr activation is responsible for nicotine's therapeutic actions in these "nicotine-responsive" disorders (Decker MW et al, Life Sci, 56: 545-570, 1995), it is clear that,

like many other drugs, nicotine has complex neuropharmacological effects. Thus, many people with such nicotine-responsive disorders, could be helped with a nAChr blocker which has been illustrated by the present invention describing how mecamylamine, a nAChr blocker, reduced the symptoms in the nicotine responsive disorders, TS and ADHD.

Schizophrenia, a psychiatric disorder involving hyperdopaminergic tone, is most often treated with neuroleptics, but is now also thought to be a nicotine-responsive disorder. For example, surveys of schizophrenic patients have demonstrated rates of smoking between 74% and 92%, compared to 35% to 54% for all psychiatric patients and 30%-35% for the general population. It has been speculated that cigarette smoking may improve underlying psychopathology by enhancing concentration and reducing anxiety from hyperarousal (Gopalaswamy AK, Morgan R, Br J Psychiatry, 149: 523, 1986). In addition, nicotine may have some role to play in reducing the cognitive deficits associated with schizophrenia and neuroleptic treatment. Cigarette smoking has been found to normalize sensory gating deficits in schizophrenic patients (Adler LE et al, Am J Psychiatry 150:1856-1861, 1993) and a recent study found that transdermal nicotine reversed some of the adverse cognitive effects of standard anti-psychotic medication and improved cognitive performance in general for schizophrenic patients (Levin ED et al, Psychopharmacology 123:55-63, 1996). If as we now hypothesize that nicotine administration may actually have a similar effect as a nAChr blocker, then it is possible that a nAChr blocker such as mecamylamine and related compounds would also reverse the adverse cognitive effects of the anti-psychotic medication and improve cognitive performance in schizophrenic patients. Moreover, since nicotine potentiates the therapeutic effects of neuroleptics in TS (McConville BJ et al, Biological Psychiatry 31: 832-840, 1992), the use of mecamylamine as an adjunct to neuroleptics in "neuroleptic-responsive" disorders such as schizophrenia and Huntington's chorea, can allow for reducing the neuroleptic dose, thereby reducing the side effects of the neuroleptic without reducing its therapeutic effects.

The foregoing description and examples are intended only to illustrate, not limit, the disclosed invention.

Claims

1. A method of treating an individual with neuropsychiatric disorders comprising administering to the individual an effective amount of a nicotine antagonist.

2. The method of claim 1 wherein the nicotine antagonist is mecamylamine or a stereoisomer or an analog thereof.

3. The method of claim 2 wherein the effective amount of mecamylamine is that which improves the individual's signs and symptoms.

4. The method of claim 3 wherein the effective amount is the amount which decreases the frequency or severity of tics in the individual.

5. The method of claim 1 comprising an additional step of administering to the individual an effective amount of a neuroleptic drug.

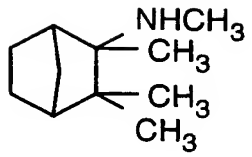
6. The method of claim 5, wherein the neuroleptic is selected from the group consisting of haloperidol, pimozide, fluphenazine, and risperidone.

7. The method of claim 1, wherein the neuropsychiatric disorder is nicotine responsive.

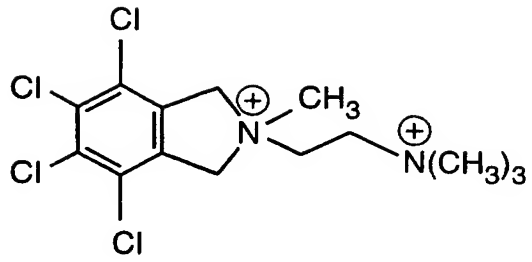
8. The method of claim 7, wherein the nicotine-responsive disorder is a movement disorder consisting of Tourette's Syndrome, essential tremors, hemidystonia, tardive dyskinesia, Parkinson's Disease and Huntington's Disease (HD).

9. The method of claim 7, wherein the nicotine-responsive disorder is schizophrenia, depression, attention deficit hyperactivity disorder, or obsessive-compulsive disorder.

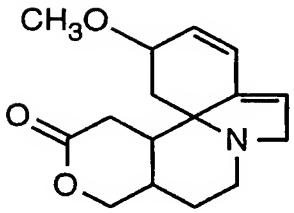
10. A method of treating an individual having Tourette's Syndrome comprising administering to the individual an effective amount of mecamylamine.



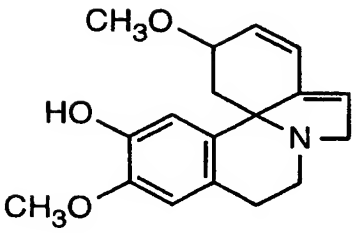
MECAMYLAMINE



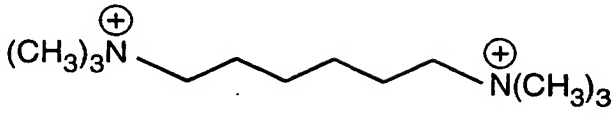
CHLORISONDAMINE



β-DIHYDROERYTHROIDINE



ERYSODINE



HEXAMETHONIUM

FIG._1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/20689

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/13, 31/445, 31/415, 31/54.
US CL :514/317, 387, 227.8, 661
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317, 387, 227.8, 661

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,574,052 A (ROSE et al.) 12 November 1996.	1-10
A	US 5,583,140 A (BENCHERIF et al.) 10 December 1996.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 21 JANUARY 1998	Date of mailing of the international search report 27 FEB 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RAYMOND J. HENLEY III Telephone No. (703) 308-1235

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